

Chemically Induced Hepatitis After Inhaling Organic Solvents

DORIAN H. CORDES, MD, MPH

WILLIAM D. BROWN, PhD, MD

Tucson

KEVIN M. QUINN, MD

Red Oak, Iowa

LIVER INJURIES have been associated with accidental and occupational exposure to chemicals.¹⁻⁴ Epidemiologic studies, however, have not always shown abnormalities of liver function associated with exposure to organic solvents.⁵⁻⁷ The pathologic mechanism underlying the hepatic injury has usually been studied in cases involving a single massive exposure. Most occupational exposures are less than massive and may involve an ongoing exposure to many compounds simultaneously and repeatedly. We report two cases of chemically induced hepatitis resulting from inhalational exposure to methylene chloride alone in one case and to a mixture of organic solvents in another.

Reports of Cases

Case 1

The patient, a 50-year-old man with a history of pancreatitis and cholecystectomy some 15 years before admission but otherwise in good health, was admitted to hospital for evaluation of a temperature of 39.4°C (103°F). The patient appeared ill but had no localizing signs of infection on physical examination. The liver was palpable but not enlarged or tender. The results of initial laboratory studies were normal except for a leukocyte count of 4,900 per μ l with a left shift (75% segmented neutrophils, 10% band forms, 13% lymphocytes, and 1% monocytes) and elevated serum enzyme levels: alkaline phosphatase 142 IU per liter (normal 29 to 93), lactic dehydrogenase (LDH) 266 IU per liter (normal 85 to 156), and serum aspartate aminotransferase (AST, formerly SGOT) 66 IU per liter (normal 10 to 35). Laboratory tests for hepatitis A and B antibodies were negative. Further evaluation, including an abdominal computed tomographic scan, abdominal ultrasound, and abdominal and chest radiographs, failed to reveal any abnormalities except for a surgically absent gallbladder. Blood and urine cultures were negative. Therapy with cefazolin sodium was initiated empirically, and over the ensuing 24 hours the patient's temperature returned to normal. He was discharged five days after admission.

Additional history from the patient subsequently revealed that he had been employed as a materials laboratory technician for about two months. Before this job he had no notable exposure to chemical solvents. His job included a laboratory

procedure for extracting asphalt using methylene chloride. Normally this procedure was carried out inside a hood. Personal protective equipment was not worn. Two days before admission, the patient was involved in this extraction procedure when a leaking gasket in the reaction vessel led to a spill of methylene chloride. Between two and four quarts of methylene chloride spilled onto the floor. Methylene chloride also spilled onto the patient's hands, legs, and feet. The methylene chloride was slightly warm. The patient cleaned up the spilled solvent with rags without gloves and disposed of them outside the laboratory in a waste container. The cleanup process took five to ten minutes. His soiled clothing and shoes were not changed and were worn another two to three hours until finishing the work shift and for an additional hour while driving home. The laboratory was kept closed; the ventilation hood was operating. The total actual and potential exposure to methylene chloride, therefore, was about four hours.

Following the cleanup, the patient continued to work in the laboratory for the rest of his normal work shift despite the fact that later the same day he noticed that he was nauseated, felt warm, and had a headache. During the night following the incident, the patient described symptoms of a flulike syndrome, including chills, headache, and nausea. During the next day, the patient noted continuing chills and headache but was able to complete his work shift. That night he awoke with fever, nausea, and a more severe headache. He was admitted to hospital the following day.

This patient had never smoked, admitted drinking five to six beers per week, and jogged four to five miles (6.4 to 8.0 km) per day. He was close to his ideal weight and exercised dietary restraints on cholesterol. He was taking no drugs known to be hepatotoxins.

The patient subsequently has returned to his usual state of health. Table 1 shows the serial pattern in the levels of AST and LDH. The preexposure AST and LDH measurements were done during a routine medical examination.

Case 2

The patient, a 26-year-old man, was referred to an occupational health clinic for an evaluation following an exposure to several chemicals used in art layout work. The patient had been engaged in art layout work for about ten years, using various commercial products, usually similar to products used in silkscreening. About a year before presentation, the patient began a job involving decorating vinyl material that was later used in making shower curtains and mattress covers. The patient noted that ventilation in the work area was poorer than in previous jobs, and personal protective equipment was not provided. The work area was about 50 ft by 75 ft (15 m by 23 m), although much of the actual space was filled with rolls of vinyl. There were no windows and only one garage-size door, which was partially obstructed. The patient claimed to have previously witnessed a co-worker lose consciousness on one occasion when solvent odors were particularly heavy.

Four days before presentation, the patient noted symptoms of lassitude, lacrimation, mucous membrane irritation of the nose and mouth, mild chest pain, and an inability to think clearly. These symptoms did not completely resolve during time off work and, in fact, increased in severity during

(Cordes DH, Brown WD, Quinn KM: Chemically induced hepatitis after inhaling organic solvents. *West J Med* 1988 Apr; 148:458-460)

From the Environmental Preventive Occupational Health Clinic, Department of Family and Community Medicine, University of Arizona Health Sciences Center, Tucson (Drs Cordes and Brown), and the Red Oak Internal Medicine Clinic, Red Oak, Iowa (Dr Quinn).

Reprint requests to Dorian H. Cordes, MD, MPH, Department of Family and Community Medicine, Arizona Health Sciences Center, Tucson, AZ 85724.

ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
 AST = aspartate aminotransferase
 LDH = lactic dehydrogenase
 GGT = γ -glutamyl transferase

work. One day before presentation he went to a local emergency department. He was given oxygen, released, and referred. He did not return to work. When presenting to the occupational health clinic the following day, he complained of confusion, loss of memory, a burning pain in the chest and mouth, and mild shortness of breath. Additional past medical history and review of systems were noncontributory. The patient admitted to ethanol consumption on the order of one to two beers per week and smoked 1.5 packs of cigarettes per day. There was no history of the recent use of hepatotoxic drugs.

On physical examination he had only mild injection of the bulbar conjunctivae and oral mucosa. The liver was not palpable. The neurologic examination was grossly normal, without evidence of a deficit in recent or remote memory. A complete blood cell count and urinalysis were normal. The total leukocyte count was 8,400 per μ l. Blood chemistries revealed an AST level of 38 IU per liter and an alkaline phosphatase value of 96 IU per liter, both of which were slightly greater than the upper limit of normal.

A tentative diagnosis of chemical hepatitis was made. It was decided to follow this patient with serial tests of liver enzymes and restrict him from work. One week later the AST level was 38 IU per liter, the alkaline phosphatase was 106 IU per liter, and the γ -glutamyl transferase (GGT) value was 84 IU per liter (normal 8 to 52). A laboratory panel for hepatitis A and B was negative.

TABLE 1.—Serial Aspartate Aminotransferase (AST) and Lactic Dehydrogenase (LDH) Values After Exposure to Methylene Chloride, Case 1

Time of Measurement	AST, IU/liter	LDH, IU/liter
Preexposure		
7 months	36	200
Postexposure		
2 days	66	266
5 days	359	504
6 days		504
7 days	469	468
14 days	56	172
1 month	43	...
7 months	28	...

TABLE 2.—Serial Laboratory Values in Case 2

Time of Measurement	Bilirubin, mg/dl	AST, IU/liter	ALT, IU/liter	GGT, IU/liter	Alkaline Phosphatase, IU/liter
Postexposure					
1 day	0.6	38*	96*
8 days	0.9	38*	..	84*	106*
18 days	0.6	55*	..	120*	...
21 days	0.5	54*	82*	84*	99*
48 days	0.4	23	20	46	84

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT= γ -glutamyl transferase

*Above upper limits of normal.

The patient's course was complicated by the occurrence of severe right upper quadrant abdominal pain 11 days after the initial presentation. The patient was admitted to hospital for 24 hours. Physical findings were unimpressive. Abdominal radiographs and ultrasound of the gallbladder were normal. Levels of serum enzymes at that time included an AST of 55 IU per liter and alkaline phosphatase of 120 IU per liter (normal for this measurement is 50 to 136). The leukocyte count was 8,900 cells per μ l with 52% segmented neutrophils, 43% bands, and 5% monocytes. His abdominal pain spontaneously resolved, and there was no recurrence.

In an attempt to determine if the mild elevation in the liver enzyme levels noted in this patient actually represented a deficit in liver function, an indocyanine green clearance study was done three weeks after the initial presentation.

Indocyanine green was injected intravenously at a dose of 1 mg per kg. Serum specimens were collected at 5, 10, 15, and 20 minutes postinjection and quantitatively assayed for indocyanine green. The half-life for indocyanine green was 7.1 minutes. Persons with normal liver function routinely show half-lives for indocyanine green clearance of 2.5 to 3 minutes at this dose (William Dalton, MD, Arizona Cancer Center, written communication, July 1985). Liver enzyme levels measured on the same visit were elevated; the AST was 55 IU per liter, serum alanine aminotransferase (ALT, formerly SGPT) was 82 IU per liter (normal 10 to 40), GGT was 84 IU per liter, and alkaline phosphatase was 99 IU per liter. The level of bilirubin was not elevated throughout the entire course (normal 0.2 to 1.2 mg per dl), although there was a rise and fall in the total bilirubin.

The levels of AST, ALT, GGT, and alkaline phosphatase had returned to within normal limits at the next testing, 1 1/2 months following the initial visit. Repetition of the indocyanine green clearance study was planned for six months post-exposure, but the patient did not return for follow-up.

Table 2 summarizes the biochemical findings for case 2.

Additional occupational history revealed that this patient had been exposed to three products. Product A, a spray adhesive, contained 47% methylene chloride, 11% styrene polymer and copolymer, 40% propane/isobutane, and 2% unspecified hydrocarbons. Product B, a spray mat, contained unspecified quantities of methylene chloride, nitrocellulose, and butyl cellosolve, and 40% ethyl acetate/acetone. Product C, a screenwash, contained 50% acetone, 5% xylene, and 45% "nonhazardous" ingredients.

Discussion

This report documents two cases of a transient hepatitis following exposure to moderate amounts of organic solvents. The first case involved exposure to methylene chloride alone. In the second case, methylene chloride constituted a substantial portion of the total exposure; there was also significant exposure to acetone. Because both exposures involved methylene chloride, our discussion will be limited to that solvent.

Methylene chloride (dichloromethane, CH_2Cl_2) is a widely used chlorinated organic solvent. It is a nonflammable, colorless, volatile liquid with an etherlike odor. Domestic production of methylene chloride in 1984 was an estimated 584 million lb (265 million kg), with imports at about 44 million lb. It is an inert ingredient in more than 1,750 pesticide products.⁸ Methylene chloride finds wide application as a degreaser, paint remover, aerosol propellant, and

extraction solvent ("Key Chemicals: Methylene Chloride," *Chemical Engineering News*, 1980, vol 58, p 11). Therefore, the potential exists for methylene chloride exposure from a wide range of environmental sources, from industrial activities, and from the use of consumer products. Methylene chloride readily enters the body through the lungs due to its high volatility. Methylene chloride can also be absorbed through the skin in significant amounts.⁹ Methylene chloride is a known hepatotoxin in both humans¹⁰⁻¹² and animals.¹³⁻¹⁵ Methylene chloride is metabolized producing carbon monoxide. The production of carbon monoxide is responsible for most of the acute effects of methylene chloride intoxication, and the severity of an acute exposure can be assessed by determining carboxyhemoglobin levels.

Both of the cases presented satisfy the criteria for occupationally induced illness.¹⁶ Our first purpose in presenting them is as a reminder that occupational diseases do not usually present with unique findings that allow easy differentiation from nonoccupational causes. The possibility of an occupational disease can result in both an inaccurate diagnosis and inappropriate treatment. In addition, the patient may be denied the benefits of financial compensation for work-related illnesses.

Second, these cases involve chemically induced hepatitis, a phenomenon whose incidence rate is largely undefined. It may well be that many cases are mild and go unrecognized. Cases involving only mild elevation in liver enzyme levels may be attributed to other factors, including spurious laboratory results. When detected, abnormalities in liver studies should be observed for a return to normal. Laboratory studies providing a more sensitive assessment of liver function include the indocyanine green clearance test,¹⁷ the antipyrine clearance test,¹⁸ and fasting levels of serum bile acids.¹⁹ Workers with confirmed solvent-induced chemical hepatitis may not be able to return to occupations that expose them to hepatotoxic chemicals, as persistent clinical sensitivity will result in the rapid development of hepatitis following reexposure.

The risk of long-term sequelae from transient liver injury is unknown. In the case of methylene chloride, recent data suggest a potential for carcinogenicity in animals.²⁰ Where a medical surveillance of workers is done, evaluation of hepatic status, including medical and occupational history, physical examination, and appropriate laboratory studies, should be part of the program for workers exposed to known hepatotoxins.

REFERENCES

1. Popper H, Gerber A, Schaffner F, et al: Environmental hepatic injury in man. In Popper H, Schaffner F (Eds): *Progress in Liver Diseases*, Vol 6. New York, Grune & Stratton, 1979, pp 605-638
2. Hutchins KS, Kung M: 'Experimentation' with chloroform. *Am J Med* 1985; 78:715-718
3. Sotaniemi EA, Sutinen S, Arranto AJ, et al: Liver injury in subjects exposed occupationally to chemicals in low doses. *Acta Med Scand* 1982; 212:207-215
4. Dossing M, Ranek L: Isolated liver damage in chemical workers. *Br J Ind Med* 1984; 41:142-144
5. Pond SM: Effects on the liver of chemicals encountered in the workplace. In *Occupational disease—New vistas for medicine*. *West J Med* 1982; 137:506-514
6. Kurppa K, Husman K: Car painters' exposure to a mixture of organic solvents—Serum activities of liver enzymes. *Scand J Work Environ Health* 1982; 8:137-140
7. Lundberg I, Hakansson M: Normal serum activities of liver enzymes in Swedish paint industry workers with heavy exposure to organic solvents. *Br J Ind Med* 1985; 42:596-600
8. EPA probes methylene chloride. *Environ Health Lett* 1985; 24:3
9. Stewart RD, Dodd HC: Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride, and 1,1,1-trichloroethane through the human skin. *Am Ind Hyg J* 1964; 25:439-446
10. Condie LW, Smallwood CL, Laurie RD: Comparative renal and hepatotoxicity of halomethanes: Bromodichloromethane, bromoform, chloroform, dibromochloromethane, and methylene chloride. *Drug Chem Toxicol* 1983; 6:563-578
11. Memon NA, Davidson AR: Multisystem disorder after exposure to paint stripper (Nitromors). *Br Med J [Clin Res]* 1981; 282:1033-1034
12. Puurunen J, Sotaniemi E: Usefulness of follow-up liver-function tests after dichloromethane exposure (Letter). *Lancet* 1985; 1:822
13. Kjellstrand P, Bjerkemo M, Adler-Maihofer M, et al: Effects of methylene chloride on body and organ weight and plasma butyrylcholinesterase activity in mice. *Acta Pharmacol Toxicol (Copenh)* 1986; 59:73-79
14. Burek JD, Nitschke KD, Bell TJ, et al: Methylene chloride: A two-year inhalation toxicity and oncogenicity study in rats and hamsters. *Fundam Appl Toxicol* 1984; 4:30-47
15. Balmer MF, Smith FA, Leach LJ, et al: Effects in the liver of methylene chloride inhaled alone and with ethyl alcohol. *Am Ind Hyg Assoc J* 1976; 37:345-352
16. Rest KM, Hake JC, Cordes DH: The Occupational and Environmental History—Project Module. Health Resources Administration Contract No. 232-78-0191, August 1983, p 14
17. Gilmore IT, Marigold JH, Thompson RPH: Half-life time of clearance of indocyanine green in patients with liver disease. *Hepato-gastroenterol* 1982; 29:55-57
18. Dossing M: Noninvasive assessment of microsomal enzyme activity in occupational medicine. *Int Arch Occup Environ Health* 1984; 53:205-218
19. Liss GM, Greenberg RA, Tamburro CH: Use of serum bile acids in the identification of vinyl chloride hepatotoxicity. *Am J Med* 1985; 78:68-76
20. Toxicology and Carcinogenesis Studies of Dichloromethane in F344/N Rats and B6C3F1 Mice, US Department of Health and Human Services, National Institutes of Health publication No. 86-2562. Research Triangle Park, National Toxicology Program, 1986

Blastomycosis in Saskatchewan

VINOD VALLABH, MD, FRCP(C)
TOM MARTIN, MA
JOHN M. CONLY, MD, CCFP, FRCP(C)
Saskatoon, Saskatchewan

BLASTOMYCOSIS, caused by the dimorphic fungus *Blastomyces dermatitidis*, is endemic along the Mississippi, Missouri, and Ohio river basins in the United States and in Manitoba, Quebec, and an area north and east of Lake Superior in Ontario.¹⁻³ The natural habitat of this organism remains a mystery, although it has been isolated from soil on a few occasions.⁴⁻⁶ Although one case originating in Alberta was reported in 1982, blastomycosis is not known to be endemic to western Canada.⁷ We document here three cases in persons who to our knowledge had no significant residence outside Saskatchewan.

Reports of Cases

In reviewing microbiologic records at University Hospital in Saskatoon between 1972 and 1986, we found three cases in which *B dermatitidis* had been identified by either cultural or histologic means. All charts were reviewed, and, when necessary, additional information was obtained by contacting the families or attending physicians or both. Details of travel and places of residence were obtained in all cases.

Case 1

The patient, a 56-year-old power plant mechanic from Saskatoon, was admitted to hospital in March 1973 because of cough and fatigue for eight months. The cough was de-

(Vallabh V, Martin T, Conly JM: Blastomycosis in Saskatchewan. *West J Med* 1988 Apr; 148:460-462)

From the Departments of Medicine (Drs Vallabh and Conly) and Clinical Microbiology (Mr Martin and Dr Conly), University of Saskatchewan College of Medicine and University Hospital, Saskatoon. Dr Vallabh is currently affiliated with the Department of Medicine, Ottawa Civic Hospital, University of Ottawa School of Medicine, Ontario.

Reprint requests to John M. Conly, MD, Department of Medicine, University of Saskatchewan, University Hospital, Saskatoon, Saskatchewan, Canada S7N 0X0.